REMARKS

Claims 1, 2, 4-6, and 43-46 are pending in the application. Claims 1, 2, 4-6, and 43-46 stand rejected. Claim 1 has been amended. Reconsideration and allowance of Claims 1, 2, 4-6, and 43-46 is respectfully requested.

The Rejection of Claims 1-2, 4-6, and 43-46 Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 1-2, 4-6, and 43-46 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner acknowledges that the specification is enabling for methods comprising identifying the H101Y and/or S119P gamma gene mutations in a human subject and "confirming" those mutations as being associated with adult onset cerebellar ataxia in a human subject. However, the Examiner has taken the position that the specification does not enable a person skilled in the art to use the invention commensurate in scope with the claims. In particular, the Examiner asserts that the claimed invention is not directed to screening methods, and that the specification does not provide sufficient guidance with regard to which mutations embraced by the claims could actually be "confirmed" as "associated with adult onset cerebellar ataxia." Applicants respectfully disagree with the Examiner's conclusions for at least the following reasons.

While not acquiescing to the Examiner's position, but in order to clarify the claimed invention, Claim 1 has been amended and now recites:

> A method of screening for a genetic mutation that is associated with adult onset cerebellar ataxia in a human subject, said method comprising:
>
> (a) determining a first nucleic acid sequence of a human protein kinase C gamma gene from a first human subject exhibiting adult onset cerebellar ataxia;

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(b) comparing the first nucleic acid sequence to SEQ ID NO:3 to identify a difference between the first nucleic acid sequence from the first human subject exhibiting adult onset cerebellar ataxia and SEQ ID NO:3, wherein the difference alters the amino acid sequence encoded by the human protein kinase C gamma gene; and

(c) performing co-segregation analysis to determine whether the difference identified between the first nucleic acid sequence and SEQ ID NO:3 is a genetic mutation associated with adult onset cerebellar ataxia.

Support for this amendment is found throughout the specification as filed, for example at page 24, line 28; page 25, lines 25-26; and page 11, line 30, to page 13, line 24.

It is submitted that Claims 1-2, 4-6, and 43-46, as amended, are enabled by the specification as filed in view of the knowledge of the skilled artisan at the time the application was filed. It is noted that Claim 1 has been amended to clarify that the invention is directed to a *screening method* for identifying mutations associated with adult onset cerebellar ataxia in a human subject, the method comprising determining a first nucleic acid sequence of a human protein kinase C gamma gene *from a human subject exhibiting adult onset cerebellar ataxia,* comparing the first nucleic acid sequence to SEQ ID NO:3 (wild-type PRKCG sequence), to identify a difference between the first nucleic acid sequence and SEQ ID NO:3, wherein *the difference alters the amino acid sequence encoded by the PRKCG gene*, and then *performing co-segregation analysis* to determine whether the difference between the first nucleic acid sequence and SEQ ID NO:3 is a genetic mutation associated with adult onset cerebellar ataxia.

As applicants previously noted, the specification defines the term 'genetic mutation' recited in Claim 1 step (c) as an alteration of the wild-type protein kinase C gamma (PRKCG)

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sequence deposited in GENBANK, provided as SEQ ID NO:3, that is not a recognized polymorphism (i.e., has a population frequency less than 1% in mammalian control subjects of the same species that do not exhibit ataxia). See specification at page 5, lines 1-4. It is further noted that Claim 1 recites "wherein *the difference alters the amino acid sequence encoded by the PRKCG gene.*" Therefore, Claim 1 is directed to screening for a genetic mutation in the PRKCG gene in a human subject exhibiting adult onset cerebellar ataxia, wherein the genetic mutation is not a recognized polymorphism and wherein the mutation alters the amino acid sequence encoded by the PRKCG gene.

As previously described by applicants, adequate guidance is provided in the specification which allows for one of skill in the art to identify additional mutations associated with adult onset cerebellar ataxia through routine experimentation. See applicants' response to non-final Office Action mailed on December 12, 2008, response to non-final Office Action mailed on June 15, 2007; Amendment After Final mailed on June 2, 2008; and Amendment Submitted With RCE mailed on July 29, 2008. As previously acknowledged by the Examiner, the skill level in the relevant art is high. As previously stated by the Examiner, "Given the high level of skill of one skilled in the art relevant to the claimed invention, it is clearly within the ability of such an artisan to conduct screening methods, e.g. employing samples from other types of mammals and/or patients with other types of ataxia so as to determine whether other mutations associated with ataxia exist in the protein kinase C gene of such subjects." See page 6 of non-final Office Action mailed February 15, 2007.

Moreover, as previously pointed out by applicants, the nature of experimentation required to practice the claimed invention is routine in the art, and not undue. In support of applicants' position regarding the routine nature of the experimentation required, applicants previously provided objective evidence that additional mutations in the protein kinase C gamma gene (SEQ

ID NO:3) that co-segregate with ataxia have been successfully identified by others in the field. See Nolte, D., et al., *Movement Disorders 22*(2):265-267 (2007), provided as Attachment A in the response filed by applicants on June 15, 2007, describing the identification of the mutation G63V in two human subjects exhibiting ataxia which was not detected in control chromosomes from 200 healthy subjects. In addition, as summarized in TABLE 1 of Nolte et al., numerous other mutations that co-segregate with ataxia have been identified by others in the field after the priority date of the instant invention.

The Examiner has taken the view that Nolte et al. is not relevant to the issue of enablement. Applicants disagree, and maintain the position that Nolte et al. is relevant to the enablement issue because Nolte et al. provides objective evidence supporting applicants' position regarding the routine nature of the experimentation required to practice the claimed invention, in view of the guidance provided in the instant specification.

Applicants agree with the Examiner that enablement is evaluated as of the time of filing. However, this does not preclude applicants from providing post-filing evidence which demonstrates that the claimed invention works. It is well established that post-filing evidence can be used to overcome an enablement rejection, where the post-filing evidence demonstrates that the disclosure was in fact enabling when filed, such as experimental data showing that the teachings in the application were followed to obtain a successful result. See *In re* Brana, 51 F.3d 1560, 1567 (Fed. Cir. 1995), and see also *Wands*, 858 F.2d 731. Further in this regard, it is noted that the U.S.P.T.O. Training Materials for Examining Patent Applications with Respect to 35 U.S.C. § Section 112, First Paragraph, Enablement (available at http://uspto.gov/web/offices/pac/dapp/1pecba.htm), state on page 19:

> To overcome a *prima facie* case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed,

would have enabled the claimed invention for one skilled in the art at the time of filing. This does not preclude applicant from providing a declaration after the filing date which demonstrates that the claimed invention works. However, the examiner should carefully compare the steps, materials, and conditions used in the experiments of the declaration with those disclosed in the application to make sure that they are commensurate in scope, i.e., that the experiments used the guidance in the specification as filed and what was well known to one of skill in the art. Such a showing also must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation.

Further, applicants disagree with the Examiner's assertion that the type of ataxia described in Nolte et al. is not that embraced by the claims, which require "adult onset cerebellar ataxia." Rather, it is noted that Nolte et al. describes the successful identification of additional mutations in the protein kinase C gamma gene (SEQ ID NO:3) that co-segregate with adult onset cerebellar ataxia. As described in Nolte et al., "The index patient (II/2) is presently 45 years old and came to clinical attention at age 34 because of dystonia of the right arm. . . . His father (I/2) and aunt (I/3) also suffer from mild gait ataxia and disturbed balance since age 50 and 45, respectively. Nolte at page 265, second column.

It is further noted that the experimental steps, materials, and conditions used in Nolte et al. were carried out in accordance with the detailed guidance provided in the instant specification in view of the routine methods that were well known to one of skill in the art at the time of filing the application. For example, as described in Nolte et al., all 18 exons of PRKCG were sequenced in the index patient, a heterozygous G to T missense mutation was found at position 188 in exon 2 of the gene, resulting in the substitution of glycine by valine (G63V) in

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the PRKCG protein. The same mutation was detected in the patient's father, but not in 200 healthy German controls (400 chromosomes). See Nolte et al., page 266, first column.

Therefore, it is submitted that the Nolte et al. reference provides further evidence that only routine experimentation is required to practice the method of the invention in view of the guidance in the specification and the knowledge of those of skill in the art.

Accordingly, it is demonstrated that Claims 1-2, 4-6, and 43-46, as amended, are enabled by the specification as filed in view of the knowledge of the skilled artisan at the time the application was filed. Removal of this ground of rejection is respectfully requested.

CONCLUSION

In view of the foregoing remarks, applicants submit that all of the pending claims are in condition for allowance and notification to this effect is respectfully requested. The Examiner is further requested to contact applicants' representative at 206.695.1655 to discuss any issues that may facilitate prosecution of this application.

Respectfully submitted,

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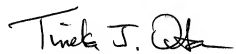

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